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10/593,683	09/20/2006	Mingjun Huang	API-0005	9081

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,683	HUANG ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,14-21,23,31,33,36 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14-21,23,31,33,36 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4 and 21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

Each species listed above corresponds to claims 4 and 21 in part.

The following claim(s) are generic: 1-3, 5-7, 14-20 and 23.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: claim 3 has been found obvious as

discussed in the rejection below. As the limitations of claim 3 are the only common features shared by the recited SEQ ID NOS of claim 4, there is no special technical feature that unifies the species corresponding to the different SEQ ID NOS.

During a telephone conversation with Anne Maxwell on 08/27/2008 a provisional election was made without traverse to prosecute the species of SEQ ID NO:1.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

The drawings filed 09/20/2006 are objected to because the three boxes in figure 1 serving as labels contain shading that obscures the text within. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top

margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 14-21, 23, 31, 33, 36 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: nucleotides in the "contacting" step of independent claims 1, 18 and 31. While the claims recite "a labeled nucleotide analog" in this step, the remaining nucleotides, labeled or unlabeled, would be required in order to synthesize an RNA transcript from the viral replicon template RNA. Applicant is advised to simply add the term "nucleotides" to the list of elements recited in the contacting step.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 7 and 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006).

With regard to claims 1 and 6, Hardy teaches:

contacting an isolated replicase complex for the positive strand RNA virus (Abstract: "A number of hepatitis C virus (HCV) proteins, including NS5B, the RNA-dependent RNA polymerase, were detected in membrane fractions from Huh7 cells containing autonomously replicating HCV RNA replicons. These membrane fractions were used in a cell-free system for the analysis of HCV RNA replication." Page 2031, column 2, last paragraph: "The P15 fractions enriched for HCV nonstructural proteins were assayed for replicase activity in the presence of a reaction mix...". Page 2030, paragraph bridging columns 1-2: "…we produced membrane fractions from cells harboring the subgenomic replicon. These fractions were shown to contain several HCV nonstructural proteins and RdRp activity. This system allows cell-free analysis of RNA replication by what is predicted to be a multicomponent HCV RNA replicase."),

an isolated viral replicon template RNA for the positive strand RNA virus (Page 2031, column 1, first paragraph of "Results": "The replicon RNA…was derived from the HCV genotype 1b…". Page 2031, column 2, last paragraph: "Since no additional RNA is added to the in vitro reaction mixture, the template corresponds to the endogenous replicon RNA."),

a labeled nucleotide analog (Page 2031, column 2, last paragraph: "…including [^{32}P]CTP…".),

and the test compound (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…".)

under conditions sufficient for in vitro RNA synthesis, to form a newly synthesized RNA population comprising the labeled nucleotide analog (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…After this preincubation period, the remaining components of the standard replication reaction were added...and the reactions continued for 1 h at 34°C.");

detecting the newly synthesized RNA population comprising the labeled nucleotide analog (See figure 7. See also Materials and Methods, paragraph entitled "In vitro HCV RNA synthesis" bridging pages 2030-2031.);

quantitating the newly synthesized RNA population comprising the labeled nucleotide analog to provide a test RNA amount (See figure 7 caption: "...quantitated by using a phosphorimager...".);

and comparing the test RNA amount with a control RNA amount of a control newly synthesized RNA population comprising the labeled nucleotide analog produced in the absence of the test compound (See figure 7; the graph clearly indicates a 0 μM inhibitor data point, which represents a reaction performed in the absence of the inhibitor, i.e. test compound.)

wherein a decrease in the test RNA amount compared to the control RNA amount indicates that the test compound inhibits RNA synthesis of the positive strand

RNA virus (See figure 7, which indicates that the amount of test RNA, as measured by the incorporation of the labeled nucleotide, decreases with increasing concentration of inhibitor.).

With regard to claims 7 and 16, Hardy teaches radiolabeled nucleotide (page 2031, column 2, last paragraph: "...including [^{32}P]CTP...").

With regard to claims 14 and 15, Hardy teaches a rhodamine derivative, which is an inhibitor of the RNA synthetic activity of the HCV NS5B protein, i.e. the viral RNA-dependent RNA polymerase (see page 2034, column 1, first paragraph). It stands to reason that since the RNA polymerase would be required for initiation of viral RNA synthesis, and inhibitor of the polymerase would also be an inhibitor of RNA synthesis initiation (meeting the limitations of claim 14). It also stands to reason that since the viral RNA polymerase is part of the replicase complex, this compound would also qualify as a replicase complex inhibitor (meeting the limitations of claim 15).

With regard to claim 17, Hardy's method of detecting comprised gel electrophoresis (page 2031, column 1, first paragraph: "RNAs were denatured with glyoxal, separated by electrophoresis on 1% agarose-phosphate gel, and visualized by autoradiography.").

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of You (US 6,004,754), Beigelman et al (US 2003/0004122) and Gauri (US 3,642,771).

The teachings of Hardy have been discussed (see rejection under 35 U.S.C. 102(b)). Hardy does not teach contacting with 2'-O-methyl-5-methyluridine-5'-triphosphate.

You teaches 2'-O-methyl-5-methyluridine as one of 19 non-naturally occurring analog of uridine (column 7, line 45 through column 8, line 6). Of the uridine analogs taught by You, only 3 comprise a 2'-O-methyl group. These are 2'-O-methyl-5-methyluridine, 2'-O-methyluridine and 2'-O-methylpseudouridine.

Beigelman teaches (paragraph [0188]): "A common approach to increase RNA stability is to replace the sugar 2'-OH group with other groups like 2'-fluoro, 2'-O-methyl

or 2'-amino. Fortunately such 2'-modified pyrimidine 5'triphosphates are shown to be substrates for RNA polymerases."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute normal uridine triphosphate, either wholly or partially, with any of the three 2'-O-methyl derivatives of urdine taught by You in order to increase the stability of the resulting RNA (e.g. to avoid RNase degradation). One would have had a reasonable expectation of success in using 2'-O-methyl-5-methyluridine since Beigelman teaches that 2'-O-methyl modification does not affect the ability of RNA polymerase to use the nucleotide as a substrate. Furthermore, Gauri teaches (column 1, lines 45-52) that 5-methyl modification of uridine (i.e. uracil) does not exhibit any virostatic activity. Thus, there would have been no reason to expect that 2'-O-methyl-5-methyluridine would not be a usable substrate for HCV RNA polymerase.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of De Francesco et al (US 2002/0164722) and Hess et al (Methods in Enzymology 200:188-204, 1991).

The teachings of Hardy have been discussed. As regards claim 3, Hardy teaches *transfecting a cell line with a viral replicon RNA or a DNA template for a viral replicon to provide a transfected cell line* (page 2030, column 1, first paragraph: "In vitro transcribed replicon RNAs are electroporated into the human hepatoma cell line Huh7 and placed under selection."). Hardy implicitly teaches *incubating the transfected cell*

line under conditions suitable for production of viral replicase complexes, since the membrane fraction obtained from the cells demonstrated replicase activity (page 2030, paragraph bridging columns 1-2: "…we produced membrane fractions from cells harboring the subgenomic replicon. These fractions were shown to contain several HCV nonstructural proteins and RdRp activity. This system allows cell-free analysis of RNA replication by what is predicted to be a multicomponent HCV RNA replicase.").

Hardy does not teach *isolating the replicase complexes and the viral replicon template RNA from the cell membrane fraction of the transfected cells*.

De Francesco teaches an in vitro method of reproducing the RNA-dependent RNA polymerase activity of the HCV NS5B protein (the replicase; see paragraph [0009]). De Francesco teaches that "…the recombinant proteins containing sequences of NS5B, either purified to apparent homogeneity or present in extracts of overproducing organisms, can catalyse the addition of ribonucleotides to the 3'-termini of exogenous RNA molecules…" (paragraph [0009]). Therefore, to purify the HCV replicase to apparent homogeneity (and thus, inherently, away from a cell membrane fraction) was known in the art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to purify the replicase *complex* from the cell membrane fraction when practicing the method of Hardy, just as De Francesco taught to do with the HCV replicase. One of skill in the art would have realized that purified proteins would have been preferable to crude cell membrane fractions, a sentiment expressed by Hess et al at page 192, last full paragraph: "In most cases, the experimental

advantages of working with purified proteins in a defined system, rather than with crude cell extracts, justify the additional effort necessary to purify the proteins in question."

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006), De Francesco et al (US 2002/0164722) and Hess et al (Methods in Enzymology 200:188-204, 1991) as applied to claim 3 above and further in view of Bartenschlager (DE19915178 A1, published October 5, 2000). As the Bartenschlager disclosure is printed in German, US Patent 6,630,343 will be relied upon as a translation.

The teachings of Hardy, De Francesco and Hess have been discussed. These reference do not teach that the DNA template for a viral replicon is SEQ ID NO:1.

Bartenschlager teaches HCV constructs for introducing into cells in order to provide autonomously replicating HCV RNA templates (see DE19915178, page 3, lines 37-46, which correlates with US Patent 6,630,343, column 3, line 66 through column 4, line 14). One of the constructs taught is Bartenschlager's SEQ ID NO:4 (see DE19915178, page 4, lines 16-21, which correlates with US Patent 6,630,343, column 5, lines 26-33), which is 100% identical to Applicant's SEQ ID NO:1 (see "Bartenschlager Sequence Alignment" provided with this Office action).

It would have been *prima facie* obvious to one of ordinary skill in the art to use the construct taught by Bartenschlager as the "subgenomic replicon" in the method of Hardy, since this sequence was designed by Bartenschlager specifically to provide HCV

replicon RNA. One of skill in the art would have considered such a modification nothing more than substituting one HCV RNA replicon construct for another. See MPEP 2144.06 regarding the obviousness of substituting equivalents.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of Favre (US 2003/0054382), Ramig et al (US 5,614,403), De Francesco et al (US 2002/0164722) and Hess et al (Methods in Enzymology 200:188-204, 1991).

The teachings of Hardy have been discussed. Hardy does not teach *incubating a positive strand RNA virus infected primary cell or cell line under conditions suitable for production of viral replicase complexes* (Hardy used cells which had been transfected, i.e. electroporated, with subgenomic HCV constructs, whereas the claim term *infected* implies the use of infectious virus to introduce the viral nucleic acid into cells). Hardy does not teach *isolating the replicase complexes and the viral replicon template RNA from the cell membrane fraction of the transfected cells*.

Favre teaches a method for "a reliable and efficient infection system for eukaryotic cells" for HCV and other viruses, wherein the cells "can be any eukaryotic cells, be they primary or from an established cell line" (paragraphs [0095]-[0098]).

Ramig demonstrates that it was known in the art to purify viral replicase complexes from infected cells (column 2, lines 12-15): "…studies of replicase complexes isolated from infected cells show that complexes are formed that contain

viral structural and nonstructural proteins and a complete set of the (+)-sense template RNAs."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Hardy by purifying HCV replicase from cells infected by HCV (according, for example, to the method of Favre) instead of cells transfected with subgenomic HCV constructs. One of ordinary skill would have recognized this as merely an alternative source of HCV replicase complex. Although Ramig discussed a different RNA virus (rotavirus), one of skill would have realized that if cells infected with rotavirus could provide a source of purified rotavirus replicase complex, then by analogy cells infected with HCV would provide a source of purified HCV replicase complex.

De Francesco teaches an in vitro method of reproducing the RNA-dependent RNA polymerase activity of the HCV NS5B protein (the replicase; see paragraph [0009]). De Francesco teaches that "…the recombinant proteins containing sequences of NS5B, either purified to apparent homogeneity or present in extracts of overproducing organisms, can catalyse the addition of ribonucleotides to the 3'-termini of exogenous RNA molecules…" (paragraph [0009]). Therefore, to purify the HCV replicase to apparent homogeneity (and thus, inherently, away from a cell membrane fraction) was known in the art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to purify the replicase *complex* from the cell membrane fraction when practicing the method of suggested by the combined teachings of Hardy,

Favre and Ramig, just as De Francesco taught to do with the HCV replicase. One of skill in the art would have realized that purified proteins would have been preferable to crude cell membrane fractions, a sentiment expressed by Hess et al at page 192, last full paragraph: "In most cases, the experimental advantages of working with purified proteins in a defined system, rather than with crude cell extracts, justify the additional effort necessary to purify the proteins in question."

Conclusion

Claims 18-21, 23, 31, 33, 36 and 51 are allowable over the prior art. Independent claims 18 and 31 define a method using an isolated replicase complex from a virus, a template, and labeled nucleotide analog to form a labeled RNA transcript, which is then hybridized to a probe that is complementary to at least a portion of the transcription initiation region, and treated with ribonuclease. Hence the probe protects a portion of the labeled transcript in the region of transcription initiation, which can then be quantitated to assess the newly initiated RNA (as opposed to RNA that had already been formed or was in the process of being formed at the time the viral replicase complex was isolated, which would thus only incorporate label in a region of the transcript distal to the initiation region).

It was known in the prior art to use an RNase protection assay to map the transcription start site, and such an assay could also be used to determine the amount of a particular transcript in a sample (e.g. see Gifford et al, Journal of Bacteriology 182(19):5416-5424, October 2000). However, in such assays, it is the *probe* that is labeled, not the transcript being analyzed. Thus, where it might have been obvious to

use an RNase protection assay to determine the amount of transcript produced by the HCV replicase in the method of Hardy et al, one would *not* have included a labeled nucleotide in the replicase reaction, as is required by the instant claims. Instead, one would have used unlabeled nucleotides in the replicase reaction, and hybridized the products of that reaction to a labeled probe.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637